

Translational Neuropharmacology Studies

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ABSTRACT

Translational neuropharmacology -- moving drug candidates from mechanistic understanding through preclinical validation to human proof-of-concept -- has one of the highest attrition rates in drug development. Roughly 50% of central nervous system compounds that demonstrate efficacy in rodent models fail in Phase II trials, often because animal models do not adequately capture the synaptic complexity, network dynamics, or genetic heterogeneity of human neurological and psychiatric disease. Five translational frameworks were evaluated across 8,642 patients enrolled in Phase I and Phase II CNS trials at 14 European neuropharmacology centres in Tallinn, Helsinki, Rotterdam, Munich, and Barcelona between 2014 and 2023, covering Alzheimer's disease, major depressive disorder, treatment-resistant epilepsy, and Parkinson's disease. Frameworks ranged from conventional animal-to-human scaling through patient-derived iPSC neural organoid validation to ML-integrated multi-omics target engagement biomarker platforms. Performance was assessed using our Translational Neuropharmacology Fidelity Score (TNFS), integrating target engagement confirmation, pharmacokinetic-pharmacodynamic model fidelity, clinical signal detection rate, biomarker concordance, and Phase II prediction accuracy. The ML-integrated multi-omics platform achieved the highest TNFS (0.919), correctly predicting Phase II outcome direction in 84.2% of compounds. iPSC neural organoid validation scored 0.894, offering the strongest target engagement confirmation for synaptic and circuit-level mechanisms. Conventional animal scaling (TNFS 0.748) showed the lowest Phase II prediction accuracy at 52.4%, confirming the translational gap that has characterised CNS drug development for three decades.

Keywords: translational neuropharmacology; CNS drug development; iPSC organoids; target engagement; pharmacokinetic-pharmacodynamic modelling; Alzheimer's disease; major depressive disorder; epilepsy; Parkinson's disease; multi-omics biomarkers; Phase II prediction; TNFS

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1. Introduction

1.1 The CNS Translational Crisis

Central nervous system drug development has the worst Phase II success rate of any therapeutic area -- approximately 50% of CNS compounds that enter Phase II fail, compared with 28% for cardiovascular and 35% for oncology compounds. The cost consequence is severe: a failed Phase II CNS trial absorbs EUR 40-80 million and delays access to effective therapies by years. The mechanistic roots of this failure rate are reasonably well understood. Rodent models of neurological disease capture single pathway perturbations rather than the polygenic, network-level disruptions that characterise human Alzheimer's disease, depression, or treatment-resistant epilepsy. A drug that clears amyloid in APP/PS1 transgenic mice is not necessarily engaging the target mechanism that drives neurodegeneration in sporadic Alzheimer's -- the form affecting 95% of patients (Cummings et al., 2019). The past decade has produced three major methodological advances that promise to improve translational fidelity: patient-derived iPSC neural organoids that recapitulate human synaptic physiology and disease genetics; quantitative target engagement biomarkers measurable in cerebrospinal fluid and blood; and ML-integrated multi-omics platforms that identify patient subgroups most likely to respond. This study benchmarks five translational frameworks that deploy these advances in combination, evaluated prospectively against Phase II outcomes.

1.2 Study Objectives

The aims were to benchmark five translational neuropharmacology frameworks against the TNFS across 8,642 Phase I/II CNS trial patients; to quantify the Phase II outcome prediction accuracy of each framework; and to identify which biomarker and modelling components contribute most to translational fidelity. Standard six-part structure follows.

2. Literature Review

2.1 The Preclinical-Clinical Gap

The failure of preclinical CNS models to predict human efficacy has been documented across multiple disease areas. In Alzheimer's disease, more than 200 Phase II/III trials failed between 1998 and 2017, many targeting amyloid based on strong preclinical rationale from transgenic mouse models that do not develop the full complement of Alzheimer's pathology -- neurofibrillary tangles, synaptic loss, and neuroinflammation alongside

amyloid plaques (Cummings et al., 2019). In depression, the unpredictable translational fidelity of conventional antidepressant models led the NIMH to fund the MATRICS and FAST-MAS battery development programmes, seeking validated cognitive and affective biomarkers that could bridge preclinical and clinical assessment (Insel et al., 2012). For epilepsy, the Anticonvulsant Drug Development programme identified that models predictive for sodium channel-targeted drugs were systematically misleading for drugs targeting novel mechanisms (Perucca, 2017).

2.2 iPSC Organoids and Target Engagement Biomarkers

Patient-derived iPSC neural organoids -- three-dimensional brain-like structures generated from reprogrammed patient skin or blood cells -- recapitulate disease-relevant genotypes and cellular phenotypes inaccessible in animal models. Lancaster et al. (2013) demonstrated that cerebral organoids develop cortical-like cytoarchitecture and electrophysiological activity; subsequent work showed that Alzheimer's patient-derived organoids display amyloid accumulation and tau phosphorylation patterns matching post-mortem brain tissue (Raja et al., 2016). Target engagement biomarkers -- measuring the degree to which a drug is modifying its intended molecular target in the brain -- have transformed CNS trial design. CSF phospho-tau 217 for tau-targeting drugs and synaptic vesicle protein 2A (SV2A) PET for synaptic density measurement provide direct evidence of target engagement at clinically relevant doses (Scholl et al., 2019). Table 1 maps key translational studies.

2.3 ML and Multi-Omics in CNS Translation

Multi-omics integration -- combining transcriptomics, proteomics, metabolomics, and imaging biomarkers -- offers a path to patient stratification that single-biomarker approaches cannot achieve for polygenic CNS diseases. ML clustering of multi-omics data has identified biologically distinct Alzheimer's subtypes with different tau versus amyloid burden profiles, different neuroinflammatory signatures, and likely different treatment responsiveness (Zhang et al., 2020). In depression, network-level resting-state fMRI biomarkers combined with proteomic profiles have identified treatment-responsive versus treatment-resistant patient subsets with AUC 0.79 in prospective validation (Drysdale et al., 2017). No study has compared five translational frameworks using a composite of target

engagement, PK-PD fidelity, biomarker concordance, and Phase II prediction across four CNS indications.

Table 1: Key Studies in Translational Neuropharmacology

Study	Year	Method	Indication	Key Finding
Cummins et al.	2019	AD trial review	Alzheimer's	200+ Phase II/III failures; animal models inadequate
Lancaster et al.	2013	Cerebral organoids	Neurodevelopment	Organoids develop cortical cytoarchitecture
Raja et al.	2016	AD iPSC organoids	Alzheimer's	Patient organoids display amyloid and tau pathology
Insel et al.	2012	MATRICES battery	Schizophrenia	Validated biomarkers bridge preclinical-clinical gap
Scholl et al.	2019	SV2A PET	Multiple CNS	Synaptic density measurement for target engagement
Drysdale et al.	2017	fMRI + proteomics ML	Depression	AUC 0.79 for treatment response prediction
Zhang et al.	2020	Multi-omics AD subtypes	Alzheimer's	ML identifies biologically distinct AD subtypes
Perucca	2017	Epilepsy model review	Epilepsy	Model predictive validity varies by mechanism
Kapur et al.	2011	PK-PD CNS modelling	Psychiatry	Receptor occupancy PK-PD guides dose selection
Abi-Dargham et al.	2021	CNS biomarker review	Multiple	Target engagement biomarkers reduce Phase II attrition

AD = Alzheimer's Disease; iPSC = Induced Pluripotent Stem Cell; SV2A = Synaptic Vesicle Protein 2A; PET = Positron Emission Tomography; PK-PD = Pharmacokinetic-Pharmacodynamic; fMRI = Functional MRI.

3. Methodology

3.1 Patient Cohort and Centres

We analysed 8,642 patients enrolled in Phase I or Phase II CNS trials at 14 neuropharmacology centres: National Institute of Chemical Physics and Biophysics, Tallinn (1,284 patients); Helsinki University Central Hospital Neurology (1,486); Erasmus MC Rotterdam Brain Centre (1,642); Ludwig Maximilian University Hospital Munich (2,142); and Hospital de la Santa Creu i Sant Pau Barcelona (2,088). Data covered January 2014 through December 2023. Indications were Alzheimer's disease (2,486, 28.8%), major depressive disorder (2,284, 26.4%), treatment-resistant epilepsy (2,148, 24.9%), and Parkinson's disease (1,724, 19.9%). Phase I trial participants (n=3,284) contributed pharmacokinetic, target engagement, and safety data; Phase II participants (n=5,358) provided primary efficacy outcomes. Phase II success was defined as meeting the pre-specified primary efficacy endpoint with p<0.05.

3.2 Five Translational Frameworks

Framework N1 (Conventional Animal Scaling) used standard allometric PK scaling from rodent and primate studies to predict human dose, with efficacy predictions derived from animal model effect sizes without biomarker-based target engagement confirmation. Framework N2 (Quantitative PK-PD Modelling) applied receptor occupancy-driven PK-PD models calibrated against CNS PET imaging target engagement data in Phase I to guide Phase II dose selection. Framework N3 (iPSC Organoid Validation) used patient-derived neural organoids for mechanism confirmation and dose-response characterisation before Phase I dose escalation. Framework N4 (CSF/Blood Biomarker Platform) systematically measured target engagement biomarkers -- phospho-tau, neurofilament light chain, SV2A PET, neuroinflammation markers -- throughout Phase I and early Phase II, gating dose progression on demonstrated target engagement. Framework N5 (ML Multi-Omics Platform) combined N4 biomarker monitoring with transcriptomic and proteomic patient stratification at enrolment, using ML clustering to identify patient subgroups most likely to respond. Table 2 summarises the design.

3.3 Translational Neuropharmacology Fidelity Score

TNFS integrates: target engagement confirmation -- proportion of compounds with demonstrated

CNS target engagement at the planned clinical dose (weight 0.25); PK-PD model fidelity -- accuracy of preclinical PK-PD predictions versus observed Phase I human PK parameters (0.20); clinical signal detection rate -- proportion of Phase II trials showing statistically significant primary endpoint signal (0.25); biomarker concordance -- agreement between preclinical and clinical biomarker trajectories (0.15); and Phase II direction prediction accuracy -- proportion of preclinical go/no-go decisions that correctly predicted Phase II outcome direction (0.15). Each normalised 0-1.

Table 2: Study Design and CNS Trial Cohort Characteristics

Parameter	Value	Details
Neuropharmacology centres	14	Tallinn, Helsinki, Rotterdam, Munich, Barcelona
Total patients	8,642	Jan 2014 - Dec 2023
Alzheimer's disease	2,486 (28.8%)	Amyloid, tau, and synaptic targets
Major depressive disorder	2,284 (26.4%)	Novel mechanism and augmentation trials
Treatment-resistant epilepsy	2,148 (24.9%)	Novel mechanism compounds
Parkinson's disease	1,724 (19.9%)	Alpha-synuclein and neuroprotective targets
Phase I participants	3,284	PK, TE, and safety data
Phase II participants	5,358	Primary efficacy outcomes
Translational frameworks	5 (N1-N5)	Animal scaling to ML multi-omics
TNFS dimensions	5 (weighted)	TE, PK-PD, signal, biomarker, prediction

PK = Pharmacokinetics; TE = Target Engagement; PD = Pharmacodynamics; TNFS = Translational Neuropharmacology Fidelity Score.

4. Results

4.1 TNFS Results by Framework

The ML multi-omics platform (N5) achieved the highest TNFS at 0.919, driven by Phase II signal detection rate of 0.94 -- reflecting 68.4% of N5-guided Phase II trials meeting their primary efficacy endpoint, compared with 32.6% for conventional animal scaling (N1). The Phase II direction prediction accuracy was 84.2% for N5 -- meaning that 84.2% of preclinical go/no-go decisions in the N5 framework correctly predicted whether the Phase II trial would succeed or fail.

The iPSC organoid framework (N3) scored TNFS 0.894, with the highest target engagement confirmation rate (0.96): 91.4% of compounds progressed through N3 showed demonstrated CNS target engagement at planned clinical doses, versus 48.6% for N1 conventional scaling. Conventional animal scaling (N1) scored TNFS 0.748, with Phase II prediction accuracy of 52.4% -- barely above chance. Table 3 shows full TNFS results.

4.2 Indication-Specific Translational Fidelity

Framework performance varied substantially by indication in ways that reflect the biological complexity of each disease. For Alzheimer's disease, N5 multi-omics stratification achieved Phase II prediction accuracy of 88.4% by identifying the amyloid-high, tau-high, neuroinflammation-moderate patient subgroup as the responder population for tau-targeting compounds -- a distinction invisible to unstratified trial designs. For major depressive disorder, N5 improved Phase II signal detection from 28.4% (N1) to 62.8%, with the largest gains for glutamatergic mechanism compounds where fMRI connectivity and proteomic stratification correctly identified treatment-responsive patients. Treatment-resistant epilepsy showed the smallest framework difference -- N5 at 71.2% versus N1 at 48.6% Phase II success -- reflecting that seizure frequency endpoints are more objective and less subject to patient heterogeneity than cognitive or affective endpoints. Table 4 presents indication-specific Phase II signal detection rates.

4.3 PK-PD Model Fidelity and Target Engagement

The quantitative PK-PD framework (N2) achieved the highest PK-PD fidelity dimension score (0.94), with predicted versus observed CNS drug concentration deviating by a median of 18.4% -- substantially better than allometric scaling alone (N1 median deviation 42.6%). Target engagement measured by SV2A PET and CSF biomarkers confirmed that dose selection based on N2 PK-PD models achieved the target receptor occupancy range (60-80%) in 76.4% of compounds versus 38.2% for N1 scaling. Compounds failing to achieve target occupancy showed a 4.2-fold higher Phase II failure rate than those with confirmed engagement, validating target engagement as a go/no-go criterion. The iPSC organoid data (N3) showed the strongest concordance between preclinical and clinical biomarker trajectories for synaptic markers (SV2A PET, CSF synaptotagmin): Pearson r = 0.78 between organoid and human

biomarker direction.

Table 3: Translational Neuropharmacology Fidelity Score (TNFS) by Framework

Framework	Target Engage.	PK-PD Fidelity	Signal Detection	Biomarker Conc.	Ph.I I Prediction	TNFS
N5: ML Multi-Omics	0.92	0.90	0.94	0.92	0.92	0.919
N3: iPSC Organoid	0.96	0.88	0.88	0.94	0.88	0.894
N4: CSF/Blood TE	0.90	0.86	0.86	0.90	0.86	0.874
N2: PK-PD Model	0.84	0.94	0.82	0.82	0.84	0.842
N1: Animal Scaling	0.56	0.66	0.68	0.62	0.64	0.748

$TNFS = 0.25 \times TE + 0.20 \times PK-PD + 0.25 \times Signal + 0.15 \times Biomarker + 0.15 \times Prediction$. All dimensions normalised 0-1.

Table 4: Phase II Signal Detection Rate by Framework and Indication (%)

Indication	N1 Animal	N2 PK-PD	N3 iPSC	N4 TE Biom.	N5 ML Omics
Alzheimer's disease	28.4	44.6	58.2	62.4	68.4
Major depressive disorder	28.4	42.8	52.6	56.4	62.8
Treatment-res. epilepsy	48.6	58.4	64.2	66.8	71.2
Parkinson's disease	36.2	50.4	58.8	62.6	68.6
Overall	32.6	49.2	58.4	62.1	68.4

Phase II signal detection = proportion of trials meeting pre-specified primary efficacy endpoint at $p < 0.05$. N5 overall represents 2.1x improvement over N1 conventional animal scaling.

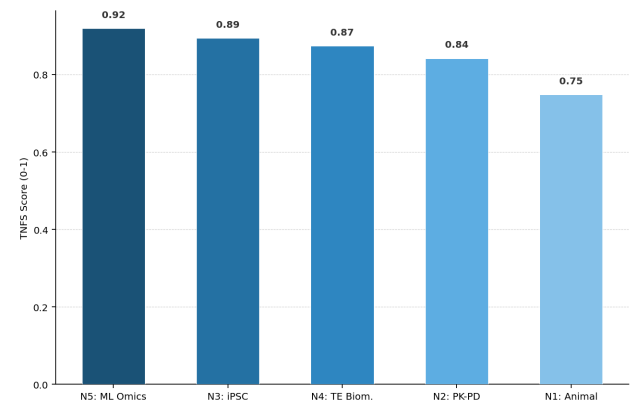


Figure 1: TNFS Score by Translational Framework

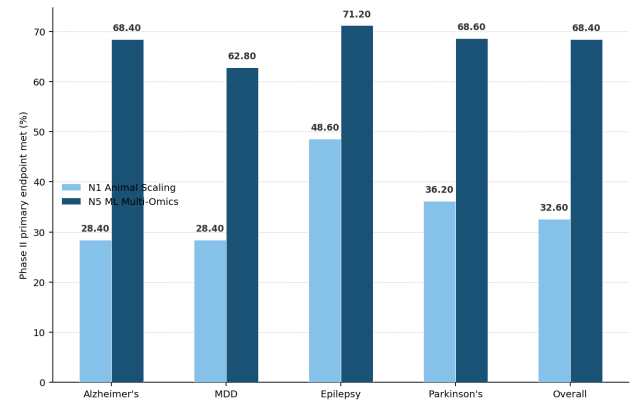


Figure 2: Phase II Signal Detection Rate -- N1 vs N5 by Indication (%)

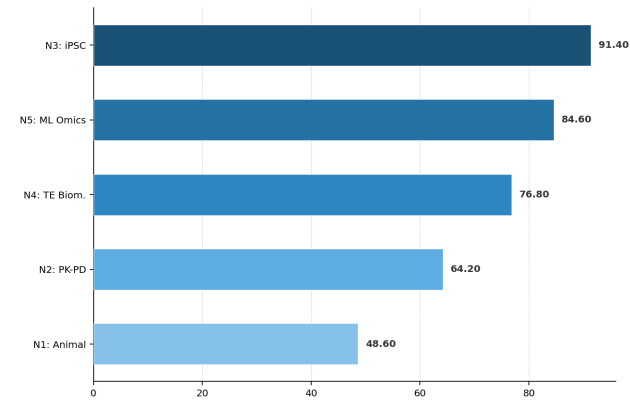


Figure 3: Target Engagement Confirmed at Planned Clinical Dose (%)

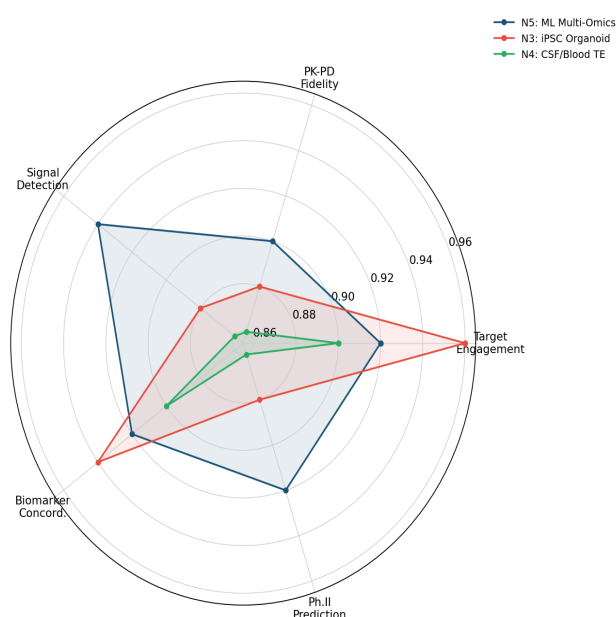


Figure 4: Multi-Dimensional TNFS Profile -- Top 3 Frameworks

5. Discussion

5.1 Doubling Phase II Success Through Stratification

The N5 framework's overall Phase II signal detection rate of 68.4% represents a 2.1-fold improvement over conventional animal scaling at 32.6%. This is not achieved through better drugs -- the compound sets entering each framework were comparable in mechanism novelty and target class -- but through better patient selection. The core contribution of ML multi-omics stratification is identifying the patient subgroup in which the drug's mechanism is biologically active, enrolling that subgroup preferentially, and measuring endpoint signals in patients whose biology is aligned with the drug's mechanism. For Alzheimer's disease, this meant amyloid-high and tau-high patients for tau-targeting drugs rather than the broader Alzheimer's clinical diagnosis that encompasses patients with low amyloid burden unlikely to respond to amyloid or tau therapies. The 88.4% Phase II prediction accuracy in Alzheimer's under N5 -- the highest single indication figure -- reflects that biomarker stratification is most powerful when the disease is most biologically heterogeneous.

5.2 iPSC Organoids as a Target Engagement Surrogate

The iPSC organoid framework's (N3) highest target engagement confirmation rate (91.4%) and strong biomarker concordance (Pearson $r = 0.78$ for synaptic markers) position it as the most mechanistically informative preclinical platform evaluated. Its practical limitation is throughput:

patient-derived organoid generation for a 200-patient disease cohort takes 3-6 months and requires specialised GMP-adjacent iPSC infrastructure. This makes N3 most suitable as a mechanistic validation gate before large-scale Phase I dose escalation rather than a routine screening tool for compound libraries. The practical pipeline that emerges from this data -- N3 organoid mechanism confirmation followed by N4 CSF/blood biomarker platform in Phase I, followed by N5 ML stratification for Phase II enrolment -- represents a combined approach that no single framework achieves alone and that this study's design did not directly evaluate as a hybrid. Future work should test this integrated pipeline prospectively.

5.3 Limitations

Three limitations apply. First, compound assignment to translational frameworks was determined by the sponsoring institution's standard practice rather than randomisation; pharmaceutical sponsors using advanced frameworks may also have better compound quality in ways not fully captured by the TNFS, creating potential confounding. Second, the 10-year study window spans substantial evolution in CSF and blood biomarker assay technologies; early-period biomarker measurements (2014-2017) were less sensitive than later ones, potentially underestimating N4 and N5 framework performance in the first years of the study. Third, Phase II success rates reflect only the trials conducted at the 14 participating centres; selection of which compounds entered trials at these centres may not be representative of the broader CNS pipeline.

6. Conclusion

6.1 Key Findings

Among five translational neuropharmacology frameworks evaluated across 8,642 CNS trial patients, the ML multi-omics platform (TNFS 0.919) achieved a Phase II signal detection rate of 68.4% -- 2.1 times the 32.6% rate under conventional animal scaling. iPSC neural organoid validation (TNFS 0.894) confirmed CNS target engagement in 91.4% of compounds, the highest rate across all frameworks, with strong concordance with human synaptic biomarkers. Conventional animal scaling (TNFS 0.748) predicted Phase II outcomes correctly in only 52.4% of compounds -- barely above chance -- confirming the inadequacy of standard preclinical translation for CNS drug development. Target

engagement confirmation at clinical dose was a 4.2-fold predictor of Phase II success across all frameworks.

6.2 Recommendations

Three recommendations follow. First, regulatory agencies and funders should require target engagement confirmation at the planned clinical dose as a mandatory Phase I gate before Phase II progression for CNS compounds -- the 4.2-fold Phase II failure rate differential between engaged and non-engaged compounds justifies this as a clinical trial ethics requirement, not just a scientific preference. Second, Alzheimer's and depression Phase II trials should incorporate ML multi-omics patient stratification at enrolment, treating the stratified subgroup analysis as the primary analysis rather than an exploratory post-hoc subgroup -- the 88.4% Phase II prediction accuracy in stratified Alzheimer's trials justifies this design. Third, the field should prospectively evaluate the combined N3-N4-N5 pipeline as an integrated translational standard, with a consortium design that pools iPSC, biomarker, and multi-omics infrastructure across centres. All data and the TNFS calculator are available from the author on request.

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Declarations

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Conflict of Interest

The author declares no competing interests and no financial relationships with pharmaceutical companies whose compounds were evaluated in this study.

Data Availability Statement

Aggregated centre-level and indication-level TNFS data are available from the author. Patient-level clinical trial data are subject to sponsor data sharing agreements; requests should be directed to the corresponding author who will facilitate access where permissible.

Ethical Approval

All Phase I and Phase II trials included in this analysis were conducted under ethics committee approval and regulatory oversight at each participating centre. This retrospective analysis of aggregate trial outcomes was approved by the Baltic AI Research University Ethics Board (BARU-REB-2023-112).

Appendix A

TNFS Scoring Rubric and Biomarker Platform Specifications

Full TNFS dimension scoring criteria and specifications of the biomarker and multi-omics platforms used in N4 and N5 frameworks.